ANTIMICROBIAL RESISTANCE

PUBLIC MEETING

PRE-APPROVAL STUDIES AND PATHOGEN LOAD

BREAKOUT GROUP DISCUSSION - AQUATICS

WEDNESDAY, FEBRUARY 23, 2000

2:00 P.M.

DOUBLETREE INN

1750 Rockville Pike

Rockville, Maryland

Randolph Room

C O N T E N T S

BREAKOUT GROUP DISCUSSION - MONOGASTRICS

February 23, 2000

Keynote: "---" indicates an inaudible in the transcript.

BREAKOUT GROUP DISCUSSION - MONOGASTRICS

(2:00 p.m.)

(Participants away from microphones.)

CHAIRMAN MacMILLAN: I'm Randy MacMillan and my official duty is to ---

DR. GOTTHARDT: I was concerned with Dr. Angulo's apparent equation of the use of medicated feeds and a subtherapeutic use of antimicrobials, and I think that's something that we really have to stress in what we take back from this breakout group is that feed as a delivery system does not necessarily mean a production, subtherapeutic use, which is more of a concern for the development of resistance.

Since I work with many minor species groups, this is an issue that's come up because, under extra label use, you can't use medicated feeds and so your therapeutic uses of medicated feeds are limited to certain industries like raising -- farm raised deer, game birds and almost all of the aquaculture industry.

And I think we really need to make the point that a therapeutic use that's short term and a good killing dose is not the threat that everyone's perceiving because I'm very concerned that this may get written up with a prohibition against medicated feed which is going to hurt these industries again.

CHAIRMAN MacMILLAN: Thank you. I agree.

(Comment away from microphone.)

CHAIRMAN MacMILLAN: I wasn't going to mention names but that's okay.

DR. BUTLER: --- that would be a different issue, wouldn't you agree?

DR. SIMMONS: The question that was raised, and I'll challenge that also -- the question that was raised, is prevention considered subtherapeutic? I would challenge that, based on the fact that I'm in complete agreement that we're going to stay away from subtherapeutic in here.

But to me, therapeutic is whether you have a disease outbreak in this particular pen and you've got a pen right next to it that doesn't have the symptoms yet but you're applying the drug at therapeutic levels.

Even though it's technically prevention, I would not let that fall into the subtherapeutic area under any way, shape or fashion because you're still with -- you know, in therapeutic fashion you've got a relatively high dose compared to subtherapeutic for a relatively short period of time.

There are -- I sat quietly for the past two days and watched all of this with a great deal of interest and I see us falling a little bit -- and the rhetoric is good and it's interesting and I'm enjoying hearing this, but I would like to give us a mandate in here to start with the ---

What are we concerned about? Obviously, in this

environment, we're concerned about water quality, whether it's in the ocean or in freshwater. What's the impact of anything that happens in that water? We're talking about antibiotic resistance so I'd like to kind of look at how we address that.

The other is, okay, are we causing resistance in the fish that would subsequently be transmitted to humans by either exposure, consumption, whatever? And the third aspect of this is, we have a mandate of these questions that the mandate, to me, assumes that pre-approval studies are necessary.

I would challenge the fact that if you go back to Fred's five things that he was throwing out, the first I would look at for all of this is what is the significance of the antibiotic in question in regard to human medicine? If it's a very important medication, then obviously we would be looking at it in a much stricter fashion.

If it's in a class that either sees limited or no use in human medicine, then we need to start taking a look at what are the true risks and I was very disturbed in the past two days of the fact that I thought I knew more about this than I think I do now and how do you design these studies has become -- we certainly raised all the issues with it.

So, there's quite a few issues to deal with but I would still focus on what's the end result that we're trying to accomplish here and that's to prevent the possibility of damage to the human.

CHAIRMAN MacMILLAN: Thank you. Is there a consensus that with regard to the use of medicated feeds? I think that's what, Joan, you were after. I don't know if we can do anything formal like a motion or anything like that but -- what's the general --

DR. GOTTHARDT: (Away from microphone.)

CHAIRMAN MacMILLAN: Right. The comment was whether or not anybody has an opinion different than that.

MS. FINEBLUM: I wouldn't say that I have an opinion different than that, but I just wanted to add in the thought of -- and this is a question; this is not a statement. Do we know what levels are going to be in the fish that's actually sick? In other words, --- certain that a sick fish from that population of fish that you're feeding the medicated feed to is actually going to ingest enough of the drug to reach adequate levels to be therapeutic and not subtherapeutic? I don't know the answer to that.

CHAIRMAN MacMILLAN: And that's a good question and it's debated an awful lot amongst animal health practitioners, and it probably is just like a terrestrial animal; it depends on how sick they are whether or not they would consume any of the medicated food.

MS. FINEBLUM: I was just going to say, the issue there goes the same way as any terrestrial and some of them don't and that's one of the problems of medicated feed per se.

But in general, if we consider at least that we're using food as a delivery system for therapeutic use and we really are not -- we're not bringing up any ideas in terms of using it as growth promotion or anything like that.

And I think one of the questions that you asked, do we need to do any at all? I think a lot of the drugs that we're looking at for fish are probably going to be offshoots of mammalian drugs anyway. I mean, usually they're -- nobody's really going into the fish market, you know, looking for exclusive drubs, at least as far as I know.

Some of those questions may be addressed already by some of the mammalian studies, but I think stability in water, binding to sediment, there are some issues that would be important to validate or, you know, define as a group here and also would be important for approvals of drugs.

Some of that might be already an environmental assessment because some of the drugs will go out into estuaries or whatever from farms that are near water. But I'm not sure how stringent those studies are and if we'd want to expand them for aquaculture use.

DR. BUTLER: I think those are critical additional pieces for --- well, just to say, I want our recorder to comment, when he's putting in comments, not to screen too much because I did suggest, there was a little bit of a difference in the waste, but that's being captured back there so it'll

come in sooner or later, won't it?

MR. PRATER: Sure. Keep me straight on these and we can go back and expand.

DR. BUTLER: Sure. We women have softer voices sometimes, but -- that's right. So I think the questions that you raised were not about -- with respect to availability in the water because if it's a binding issue and it means that the drug is perhaps more available in the water or less available, that could be a consideration in the pre-approval process.

Other than that specifically, you said the environmental assessment may or may not capture it. I don't know what your process is here so I think that's something that I have to add into my mind set when we're doing it because I know our environmental assessment does not touch that, at this point.

But in terms of antimicrobial resistance, where is the research? Is this -- I mean, we know in the land animals that a fair bit of work has been done, but fish offer that -- the use of antimicrobials in fish is perhaps a little more impacting on the environment in that you can be changing the flora, not only in and on the fish but in the water around the fish.

So people are either drinking it or swimming in it and if those bacteria that are living in the water can exchange antimicrobial resistance factors between themselves and the

humans that are either drinking or swimming in the water, that's an issue -- that's a separate issue as far as I'm concerned in antimicrobial resistance.

I'd like to hear a discussion on that possibility, quite apart from eating fish which is an issue, also.

CHAIRMAN MacMILLAN: It might be beneficial for the record to identify yourself in this group.

DR. KAZDA: My question might be a little naive since I don't know that much about fish, but I was just wondering if you talk about, you know, prudent use of antibiotics and if you put these antibiotics in the food, the feed, how can you actually control the dose that goes into the fish since some of it is going to dissolve in the water, I guess escape, and how can you know the exact amount of the antibiotics the fish will get?

CHAIRMAN MacMILLAN: Okay. Well, with some fish anyway, in the United States, we're really only talking about catfish, selmonids and now lobsters. The lobsters I don't know. With the catfish, it's more difficult than with the selmonids because you can't watch the meat as much as you can with the trout, for example.

But the fish, if they're going to eat the feed, it's very rapid and depending on the type of feeding system in that trout raceway, for example, they may be fed by demand which is where they -- does everybody know what a demand feeder is?

It's basically a cone and it has a bar attached to it and the feed is placed inside this cone, this topper, with the bar dangling down into the water. When the fish is ready to eat, it's trained so it'll knock that bar and some of the feed will drop down.

The more fish that are anxious to feed, the more that bar gets knocked. And there have been studies done that indicate that normal fish, anyway, that all that feed gets consumed. Other types of feeding systems will have a -- which is what we use, a different kind. We have a kind of a computerized feeding system where feed is taken along what's called a --- system and it goes through a cylinder and there's a die that goes back and forth and that drops small volumes of feed at any one time.

So we think, and we've done research that indicates you get more uniform feeding that way. Now with sinkfish, it's a much more difficult thing to judge and what happens typically in both catfish and trout, is that observations made of the feeding activity, if you throw feed out and it's not consumed, then you know that you shouldn't feed them anymore because it's not -- whether it's medicated or unmedicated feed, it's not fruitful to do that.

So that's basically how they do it. It's not -- there's no -- in terms of dosing the fish, there's no control like you would have if you inject -- weighed the fish and then

injected them. It's certainly not that level of sophistication.

DR. REINSCHUESSA: But as far as trying to figure out if they can achieve therapeutic concentrations in serum, I mean, those are PK studies that are done, so -- I mean, those studies were done for the approval process. So to -- and you feed under controlled conditions.

You sacrifice a certain number of them and for residues, it's absolutely essential and those methods have been validated and need to be validated to approve different species to use that antibiotic.

DR. KAZDA: So you actually measure the amount of the antibiotic and ---

DR. REINSCHUESSA: In the fish. In the fish I'm talking about.

DR. KAZDA: Okay. How about in studies --- sediment ---

DR. REINSCHUESSA: Those are studies -- right now, I know we're doing some of those studies but that one that I was mentioning would be a good thing to do if you're trying to approve an antibiotic is to find how stable is it in the water, how bioavailable is it?

Once it's bound to sediment, a lot of these compounds are no longer bioavailable for some species. I don't know about some nice --- microbe that might be able to mess with it

but, I mean, you know, you're talking a lot of research there. But that's the same issue that you deal with with chicken manure scattered on a cornfield.

CHAIRMAN MacMILLAN: Wendy, you had a --

MS. FINEBLUM: My question is whether or not anyone has ever done any behavioural studies where they've looked at a tank of fish and which you knew that there was an infection in that tank and the nature of the populations are such that not all the fish are going to be equally sick.

It's not likely that all the fish are going to be equally sick. Some are going to be sicker than others and have -- some are going to want to eat less than others. Has anyone done the behavioural studies to look and see, okay, you know, this guy, he's really sick.

How much -- you know, how often is he coming up? Maybe he's not coming up very often, and then do a sample of the population, trying to get a range of individuals based upon how sick they appear clinically and then measure the drug concentrations in these animals.

Has anything like that been before? Does it seem like a feasible project to do and do you think that the results would be useful?

DR. BUTLER: The question that you are asking is a dosing question and all of this is done in the information packs that you need to approve a drug. They have to have done

studies that say that you get this much residue after giving this much to this controlled group of fish who aren't necessarily a sick group of fish. You're right.

However, in order to -- and this is numbers of years of experience in trying to get drugs into fish -- you're right, it's not perfect, but I wonder if we could move from that piece which is interesting and important because we need to know that in terms of residues.

And in fact, the residue information because of exactly what you said, is probably very -- that much more safe because the fish, the healthy fish are eating large amounts of the medicated feed so when we do residue studies, they would probably have more of the drug in them than the sick fish.

But, in terms of changing the antimicrobial flora, those drugs would do that. The antimicrobials would change the flora of those fish. In fact, maybe you're asking that impact question about what happens to the flora of the fish which is where we need to go from here. Is that --

MS. FINEBLUM: I guess what I was getting at, more than from a residue perspective, was from the antimicrobial resistance perspective and if you're getting fish that are sick, you know they have some bacteria in their system and you're exposing them to low levels of antibiotic.

Might that create a situation where you're more likely to have resistance emerge? I don't know. But if so,

then it would be nice to know whether or not you're getting those low levels.

MR. PRATER: I think, if I might comment myself at this point, I think the question is interesting from two perspectives. One, I think you're talking about antimicrobial resistance in terms of aquatic pathogens versus human pathogens.

And I think in aquaculture, most of the time what we're concerned with are the innocent bystander, the human pathogens, because the same agents that infect the fish are not the ones that will infect the humans eventually. So it's important to distinguish which agents we're talking about becoming resistant to.

The other thing that is very well taken is your point about treating populations is very different than treating individual animals and a lot of the information has been compiled to this point, pharmacokinetic data in particular, has been done on individual animals. But really what we're treating are populations of animals, and they have sick fish as well as healthy fish.

And I think that just now people are starting to examine how we treat populations and look at things like population of pharmacokinetic parameters that describe populations of animals versus individual animals. So I think the bottom line answer to that question is only just recently,

that perspective and investigated.

DR. BUTLER: That's a nice way of articulating it. When we do treat populations, we are doing some subtherapeutic dosing which has been shown to contribute to antimicrobial resistance. It's a really important question.

But in terms of what microbes, I appreciate -- say there are enterococci in the fish, just your basic -- and I don't even know what the normal populations of bacteria are in fish but I just know bacteria are very good at treating little bits of DNA that provide antimicrobial resistance between one and the other.

So in fact, it doesn't matter which bacteria they are, whether they're actually pathogens, and this is an issue that I have with senior management in the Federal government where I work. People get confused with food poisoning and antimicrobial resistance.

And I say, well just forget the food poisoning bugs. Forget the salmonella. Forget the E.coli 0157H7. Let's just think of an enterococcus that's plain old gut bug that gets on the steak and you get it and that gives you antimicrobial resistance, so it's important to separate those issues.

I don't know the normal flora, and I'm sure it varies tremendously in fish, but it's my understanding that that ability to transmit antimicrobial resistance is certainly there and feeding at those varied levels, it's not a problem -- or it

would be a problem with fish as well as with pigs and whatever, although rarely in pigs, I guess.

Well, that must be getting more common in swine practice to be feeding medicated feed the same way as a therapeutant instead of -- yeah.

DR. REINSCHUESSA: I guess there's a couple of givens. One is antimicrobial resistance does happen with use and when you treat animals with any other form than injecting them, some of the players are going to have subtherapeutic amounts and if it's in the water, whether it came out of manure from pigs or it came from feeding fish, those levels are going to dwindle and somewhere in that curve of effluent, you're going to have a subtherapeutic amount of bacteria there.

You know, getting back to pre-approval studies, you know, what we want to do to try to predict where the problems are, how do we want to survey that later. If the outcome is, you know, you don't want to accept any risk at all, then you don't approve any of them.

But if you feel that you should be treating animals when they are sick, then what we want to do with any pre-approval work that we do for aquaculture is to try to find out where the risks are and possibly eventually find ways of mitigating the risks.

And you know, the kind of aquaculture, that is going to make a big difference. I mean, if you're at a semi-closed

or if you're at a place where you can then treat the water for a certain period of time. I mean, there are things that we can start thinking of creatively to deal with it.

You know, if we have ponds at the back of other ponds that can capture sediment and keep it from going out. But it's a given, you're going to get to that level that you have subtherapeutic amounts.

If you're treating a chicken barn and you're just giving it to them in the water, which doesn't seem so bad according to the way they're talking in there. There are some birds that are going to drink it and there are -- some of the feces is going to delude out to a point where you're going to be subtherapeutic and you're going to create resistant bugs.

But for pre-approval, I think we have to sort of figure out where do we want to go with -- with what kind of a study can help us predict the severity of that problem.

DR. BUTLER: So what do you want, Renata? What do we start with? First of all, having some baseline information on antimicrobial resistance and what normal flora are in fish would be helpful. Do you have that? Pardon my ignorance on that score.

CHAIRMAN MacMILLAN: Yeah, did you want to moderate here?

DR. BUTLER: Do you have the information?

CHAIRMAN MacMILLAN: Well actually, we do have the

information about what types of bacteria can be in the fish. It's going to be so species specific because it's so environmentally specific.

DR. BUTLER: Right.

CHAIRMAN MacMILLAN: And so, there's really no way to predict in any one given circumstance what's likely to be there. Well, I'll take that back.

DR. BUTLER: Yeah, I was going to say, if you name a species and the environment, then you would have an idea is what you just said; right?

CHAIRMAN MacMILLAN: That's correct. You will find airamonads. Okay. Airamonda hydrophelu, sobria, however they classify airamonads these days. That would be there, in the freshwater. And in saltwater, you'll find vibrio species. Sometimes you will find salmonella, if you're working with shrimp.

DR. BUTLER: Or catfish?

CHAIRMAN MacMILLAN: Catfish, you will find salmonella in those ponds. There have been some studies, published studies, on the microbial flora in various kinds of fish. I know it's been done with catfish. It's been done with striped bass.

I just saw reference to one I think in trout but I haven't seen that yet. What's going to be very -- as I mentioned in my presentation yesterday, the bacteria flora is

very itinerant. Whatever is in the water is what you're likely to find in the fish.

DR. BUTLER: Well, I appreciate your viewpoint as a producer, but as a regulator, I need to have some of that information so that I can assure the public that there is not a risk to public health.

So if I were to ask you for information, and I"m new to this pre-approval process; however, I think it's a very important one in terms of assuring that your industry can go forward and that is by saying, if we look at it in the first place, if you know it's catfish and we have these four or five species of bacteria, perhaps then you can say, okay, we will use -- and you said they're itinerant so if you even used a marker like an enterococcus with a particular antimicrobial resistance marker and did a test on that, and said treat it with -- treat these fish with this enterococci at the other end if they have antimicrobial resistance, not unlike terrestrial animals, because I need to be able to assure, in my case the Canadian public, that there isn't a risk to public health.

And if there is perceived risk -- even if there isn't a risk, if there's a perceived risk, then your industry is at stake. So I'm looking for the answers the same as you are to say, how can we look at this? What kind of study can we do that will give us some assurance?

CHAIRMAN MacMILLAN: So if I can rephrase that so I

understand, you're suggesting that we choose a bacteria that we could run through some testing.

DR. BUTLER: Well, if you have a gram positive type of bacteria -- or antibacterial, take a gram positive innocuous bacterium, inoculate the pond --

CHAIRMAN MacMILLAN: Run it through.

DR. BUTLER: -- or the fish, treat the fish, see what comes out the other end. I mean, it's the same sort of model that you would use on a terrestrial animal and we need the assurance. That's what I'm -- we need to devise a model here for you so I'm throwing out ideas.

CHAIRMAN MacMILLAN: Right, and I appreciate that. The task, of course, is that it's going to be -- in some aquacultures conditions, you're never going to see enterococci or salmonella or listeria --- so it is a bit of a task for a drug company to come up with -- or FDA to come up with choice bacteria like that. I understand the need to do that.

DR. BUTLER: Well, the recommendation should maybe come from -- the point of meeting with the CVM and industry --- you may know what the bugs are there. Let's have a recommendation because in each of the settings, if you --- you're going to have bugs in various environments, whether it's out there freezing in the ocean or in a warming pond where some catfish are growing, to come up with -- to come forward with recommendations that you try this or that so you do have some

guidance and assurance for the public. That's how I see my role.

DR. REINSCHUESSA: I guess it is a big can of worms because --- the ones in the water are not always the ones that are found on the skin. Human pathogens, some of them certainly don't need to be passage through other -- or some fish pathogens go directly to humans. They aren't necessarily always passage through something else. Fish handler's disease --- bacterium marinum.

These are not enteric pathogens, but I mean, there are some risks, so you can't just say there are no --- directly from fish to people but then, you know -- okay, if we try to say, okay, nuts and bolts, what bugs are we going to look at, you know, and I would be one for modeling as much as we can.

You know, maybe take some populations that are fairly constant like aeromonis and follow what happens in vitro, you know, in a drug with certain environmental conditions. You can grow them in warm and cold and you can grow them with salt and without salt and a lot of different -- I'm not saying aerimonis but you can pick organisms that you might be able to model.

That's going to take a lot of people thinking and working together to even pick those organisms and just trying to figure out the resistance issue is another one. And CCSL guidelines are not established for fish or for most of these bugs and the fish group that met couldn't even come up with a

reference bug, internationally.

So, we don't even know -- we don't have standards for testing resistance in a lot of these organisms yet. I mean, people do studies but, you know, you're comparing apples and oranges. You look at a lot of the different things.

You know, some people use --- you know, it all depends, and there are no standards yet. So, we're really early in the process and I think it's important to get as many people together to try and figure out what models we'd want to take.

But obviously, the ones that would be used in the PK studies, the fish that would be used and the conditions that you'd be using for those PK studies to get them started -- you know, to begin that analysis in an approval, I think those, then, you pick some bugs that would at least give us an idea where the drug would be going.

DR. GOTTHARDT: This is going to be a little bit nonsequitor here but we have something up that I want to talk about just a little bit. If you go back up a few bullets, it says therapeutic/subtherapeutic treatment regarding treatment of populations of animals and I think we need to talk about that just for a little bit because I'm not sure that the way we're using subtherapeutic is actually -- the word subtherapeutic causes a lot of concern in a lot of folks.

And when we're treating a population of animals,

especially like a flock principle, we're going to treat everybody, whether it be chickens or fish, but a certain group we're going to treat the whole group. And for CVM, we call that a controlled claim. You're treating everybody.

Some of the population is sick and some are not with the therapeutic use. It's not a subtherapeutic use as opposed to a treatment claim where all the animals are sick. So, I just wanted to differentiate on that and Bill or Maggie can chime in on that but I think it's important that we don't use the subtherapeutic term if we don't mean it.

MS. OELLER: I think that the subtherapeutic use that everyone -- well, most people are against is the production, weight gain, feed efficiency, long term use of a low dose and I think that's what the subtherapeutic term is widely used for. But, Joan's absolutely right that it can be interpreted then as just an individual animal not getting enough when the treatment is envisioned.

So I don't know if we want to say therapeutic versus production claim or something, but the point is that most of the uses we are advocating are for treatment of sick animals rather than just to make them grow faster.

DR. BUTLER: I'll be the devil's advocate again here. I appreciate what you're saying, that it's a difference between a claim, one claim and the other because it is not the intention to use the product of the growth promotant but in

fact, it is, and I'm seeing a little bit of agreement here.

And it's not the nature just of aquaculture. It's indeed, as they're treating birds and pigs the same way, we need to speak truth here to power as they say and say indeed, the nature of herd treatment means that there is indeed, although the intention is therapeutic, the outcome is therapeutic and subtherapeutic.

It's not an intentional growth promotion but in terms of engendering antimicrobial resistance, it's indeed a consideration and I think as a group of scientists, we should at least say that but be clear that the intention is not that.

MS. FINEBLUM: I would second that and I'd also like to add that perhaps what we need to is invoke a probablistic approach where we're not just using averages, we're not taking, you know, the amount the average fish would get.

We're looking at the population and treating it and understanding the variability that we're going to see within that population. And based upon that, try and predict whether or not we might see resistance come out of that.

And it could be that with such short periods of treatment that that still wouldn't happen, even though we've got a, I'll say lower than therapeutic level -- I won't say subtherapeutic -- in a particular animal.

If the period of the exposure to the drug may be so

short that you're just not likely to see resistance arise. But I would suggest that we try and get a hold of those data as well as understand the distributions in the population.

CHAIRMAN MacMILLAN: One of the questions I'd have is -- I think you're both quite right. The bacteria --- lethal concentrations of the drug. But the question is, what does that mean? So what if the bacteria developed resistance?

What does that mean from a public health perspective, and I don't know what that means and I think that's what -- as I understand one of the real -- the pre-approval studies are to try to help the people that will decide on yes or no on the drug, on the antibiotic, is whether or not that -- there is so much resistance or it's going to be such a public health problem that they can't say yes. Bill, is that --

DR. BUTLER: Do you want to speak, Bill? I had a question -- if I may be, just because I put my hand up first, before you --

CHAIRMAN MacMILLAN: Oh, okay.

DR. BUTLER: -- pointedly went over to Bill.

CHAIRMAN MacMILLAN: Well, I wasn't trying to ---

DR. BUTLER: I know but just to come back, if I could say to your comment, the antimicrobial resistance in whatever the bug is a serious issue in that, one, that piece could be -- there could be a cross-resistance.

So even though you're using an old drug that is not

used perhaps in human medicine, there may be, in that bacterium that has had that dosage and it didn't kill it and it survived, there may be a cross-resistance which represents a public health concern. That bacterium itself may not cause any problem to humans, just like the distinction between food-borne illness and antimicrobial resistance.

Simply, the transfer of the antimicrobial resistance from whatever that bacterium is sitting on the fish to the person's hand to the respiratory system, that is the public health concern. Now, if you're doing a pre-approval study, you want to know that.

So if you're treating fish and it's -- whatever the bacterium is, you treat it with that antimicrobial -- it comes up with antimicrobial resistance to that old drug or even a somewhat, you know, new mammalian treatment drug, if the cross-resistance is there, that's a serious issue and I know that we'd want to know about that and I think that's what the issue is here. I'd be happy to hear Bill's comments.

DR. FLYNN: Well, I agree with that comment about, particularly with agriculture, given the uniqueness of the pathogen or the bacteria that we're dealing with. The "direct transfer" issue may not be of great concern but then the indirect question arises which is even more complicated and a harder to get at question because of basically bug-to-bug transfer of resistance occurring there, so the pathogen -- the

bug that initially is exposed to the drug may not have any consequence for human health whatsoever but perhaps it then transfers a resistance ---

But, with regard to the pre-approval studies, I mean, I think, Randy, you're sort of suggesting that one way to look at it, it gets to the objective of the study, is a couple of ways you can look it is that, is it purely a safety study in the sense that, you know, at the end stage, you've developed a particular use, a dosage regime that is going to be administered in this fashion and you would want to test that use to see, does it present a safety, human safety problem?

It is -- can you predict whether resistance will occur under those conditions and that's one way that we've been thinking about it. Now that starts raising a lot of questions. Scientifically, can you even design such a study that can actually predict, make that prediction? I don't know.

The answer may be no, we can't really design a study. I don't know if that's the answer or not. I mean, the other thing that was talked about, the other aspect is moving sort of pre-approval studies further upstream, so to speak, in terms of drug development and can these studies help us to more direct uses that are safer than others in terms of when you consider a particular class of drug and the various different conditions --- particular species or whatever it's going to be used on, is it more or less likely to have resistance problems?

So, I guess one point to make would be that with regard to objectives, I would not limit ourselves to just thinking about these studies as studies that has to -- necessarily have to predict resistance. I mean, it would be nice if they could but maybe they can't.

And the pre-approval studies is one piece of many other -- I think other pieces that are being looked at to try to address this question, including post-approval measures which are important, too, in terms of monitoring and that kind of thing.

I mean, we've heard a lot of people say that, you know, a lot of this comes down to our ability to monitor what happens because it's very difficult to predict ahead of time. So anyway, I just -- we may want to keep open other ideas in terms of how best do we think we can use pre-approval studies?

I mean, we may come out saying that, well, we're just not there yet with the science to be able to use them for, say, predictors, or maybe we can. But, if not, then what other ways can we use them? Can we use them for optimizing how the drugs are used so that we minimize resistance? And that is -- that will fit in with perhaps other measures such as monitoring systems and that kind of thing.

DR. SIMMONS: You know, I think one of the things we keep going back to is risk and I think your concerns are very valid and I applaud the, you know, desire to ensure that we

don't enter into something that would cause us risk.

One of the things that we've got to step back and take a look at is what we're talking about is something that's been going on for probably over 2,000 years. I think the Chinese were the first to recognize that moldy curds of soybeans had antimicrobial activity.

At that time, I think the bacteria probably also were already producing betalactimeces and things of that nature. So we're not really looking at something that's new. This is probably going on all the time, whether it's terrestrial or aquatic.

The issue here is, are we changing things and causing harm and potential public health risk. And with that basis, i would ask the question, because I don't know -- if we go to Japan, Norway, several of the other countries that have been using aquaculture antibiotics for quite some time.

We also know that based on various sensitivity reports, many of the antibiotics in heavy use have developed resistance. But I'm not aware of any public health issues that have arisen from that and that would be a concern I would throw out is, first of all, let's take a look at what we know has happened already. Has anything arisen or is anybody aware of anything that has caused a problem and I don't know.

DR. REINSCHUESSA: I think you're asking a question sort of like the campylobacter risk assessment that was just

done with poultry. I mean, nobody knows exactly what's the actual risk in aquaculture. Certainly the potential is there but how -- you know, when you start evaluating the need for food, especially in third world countries and the need to produce fish in an economical way for a lot of those countries, there are risks and benefits and that's got to be looked at and I don't know who's going to do that.

DR. BUTLER: I think that's an excellent point. In some countries, it doesn't matter what you're feeding your fish or what drugs you're using on your fish because it is a matter of economics. And if they can treat the fish and keep them alive better and sell them for whatever market value.

I think our discussion here is very much a North American or Western approach in that our publics want to have food that is risk free. This is not possible. Nonetheless, we need to have food that is -- has as little risk as possible.

Indeed, I was at the December meeting where the campylobacter risk -- the model was set out, an excellent model. Does it -- the question that you ask is exactly as Renata said, exactly right. I mean, how much antimicrobial resistance is actually coming down the line and impacting on humans?

We don't know. I guess, in a sense, this is very much a trying to be on the cutting edge of public health where, instead of being reactive -- we know that there's a lot of

antimicrobial resistance out there and it's been said many times -- if you use an antibiotic, there's going to be resistance.

So if we can get some information at the outset and say, well, yeah, there's resistance but it's not resistance to important human drugs and it's important for fish production and people would accept that, I believe, if we can say that.

So it is very much a North American perspective, although we also have to be careful in speaking about other producers because, as I was joking with Renata earlier today, until I have a little made in the USA sign on the back of the fish, when you speak badly of fish, when people hear it, they want to cut down on the fish production and turn over to the tofu and the whatever else.

So, let's -- the finger pointing, in any case, is never very productive, although hopefully, North American and Western countries can lead by example. It's true, we don't know what the risk is which is what the pre-approval studies are trying to grab onto, I think.

DR. KAZDA: I did my little survey of knowledge of this issue among the general population and I can tell you that nobody that I talked to, and I have talked about quite highly educated group of people, knows that antibiotics are used in animals the way they are. I'm not even talking about --- you know.

I'm talking about agriculture in general. And so, if you are in a group of people that deal with the issue, it sounds like everybody's very much concerned but I think people in general are not concerned very much because they don't know about it, and that's not only third world countries, but that's North America I'm talking about.

CHAIRMAN MacMILLAN: Okay, Bill. I was going to say, we probably ought to try to move forward a little bit and get something concrete down so we can -- well, primarily so that tomorrow afternoon at 1:00, when I have to say what we've been talking about, or decided.

Any general comments anybody else wants to make before we really get into the meat of this thing? Okay. What's the perception of what are -- well, for aquaculture, what should pre-approval projects or research try to do? What should it try to answer?

I assume at this point, FDA has said, all right, this is going -- this is perhaps a class II type of product where we need pre-approval research done. Is that a reasonable expectation? In aquaculture, I don't think we'll ever have a class I.

In aquaculture, I don't know that we'll ever have a class II. In aquaculture, we'll be lucky if we have a class III product. Let's assume we have a class II and FDA has said, all right, you need to do pre-approval studies.

What are we looking for? What does FDA want that way? What would be most useful for FDA to make a judgment that this antibiotic is going to be reasonably safe for the public?

(No response.)

Okay. So, FDA, I guess, is still looking for guidance, somewhat --

DR. REINSCHUESSA: I mentioned stability in water.

CHAIRMAN MacMILLAN: But isn't stability in water already something that you would study?

DR. SIMMONS: I think your comments regarding the physical/chemical disposition of the agent in water is valuable information. I think that, historically, if you look at it from, again, an industrial perspective, that type of data is generated but it really wasn't generated with an antimicrobial concern; it was more of a sediment concern and issues of that type.

But I think that type of information would be pretty standard for the sponsor to develop because it's related to the stability of the agent, or that I think that that's valuable. The point I was going back to trying to do resistance studies, is, we know, for example, the potentiated sulfonamides in several markets, there's strong resistance to that where they are approved.

But yet, I'm not aware of any downstream impact and

that's where I'm trying to -- I don't have a problem generating data. What I have a problem is, how do we interpret the data we generate and that's what I'd like to do is generate meaningful data that has a endpoint to it.

DR. FLYNN: One way to try to move things would be -- and I think one, sort of the general objective is that -- and this goes back to what was put out in that guidance that CVM put out and it's been mentioned a number of times, is trying to characterize what the rate and extent of resistance development might be as a consequence of the drug use.

So I mean, if you look at that question and then you'd say, how would we go about trying to answer that question? What pieces of information would we need to make some kind of judgment about the rate and extent of resistance development and that includes -- that includes whether you're talking about direct transfer or indirect transfer, so either one would apply and in this case it may be indirect that's more of an issue.

Then, I think, looking at that general objective, what kind of information do we -- would we need to know to try to characterize them? I mean, there are some things we're going to need to know about the attributes of the drug, you know, what kind of mechanisms of resistance. Is indirect transfer likely?

So, I mean, there's a number of things to start

thinking about and how far can you get with that and sort of looking at it, also, from the putting together sort of a safety assessment where you start putting these pieces together and can you adequately characterize the risk and conclude, yeah, there's not very much risk or we're still not really sure how much risk there is so we need to then go on and get some more information.

And I think that sort of step-wise process of, you know, first -- sort of the categorization. Where does the drug that you're thinking about approving, where does it -- how important is it, relatively, to human medicine? And so -- and then move on from there in terms of looking at the attributes of the drug and other things.

And so, one way of looking at pre -- so, from a pre-approval standpoint, what kind of information would you need to get, to try to answer the general objective of characterizing the rate and extent of resistance?

DR. FINEBLUM: I have a few thoughts and I'm saying them as pretty much an outsider to this whole area, so take it for what it's worth. But, one thought that I had was, we mentioned earlier the great importance of environmental conditions to the growth of bacteria in which bacteria are going to infect or colonize a fish.

And environmental qualities like temperature and pH may be something that the producers and actually control. If

they can't be absolutely certain of the amount of drug that each individual fish is going to be getting, they can be pretty sure about what temperature the fish are at or the pH of the water is or certain other conditions.

And so, if we could understand what the likelihood of developing resistance was under various environmental conditions, we may be able to select those where it's less likely and that's something the producer has more or less control over and so that may be useful information. It just may be.

(Comments away from microphone.)

DR. FINEBLUM: And once again, this is just -- this is an idea, but you may decide that if you have sick fish that maybe it's worth having a system by which you can transfer them to some facility where those conditions can be controlled and I don't know if that's even possible, to have chutes and things where you can -- I don't know. I don't know. Not having ever visited a big trout farm before, I don't know if it's even feasible.

CHAIRMAN MacMILLAN: I can address the practical aspects of your thoughts there. It's probably -- it would take a very unique situation where they could channel fish to the hospital, so to speak, to treat that way.

Most practical fish farming, as Renata was saying, is -- you're really subject to whatever is out there in terms of

temperature, pH, carbon dioxide levels, nutrient levels, all those sorts of things.

We just don't have a good way to manipulate that environment, which is a real disadvantage. Catfish farmers have -- there's a disease that they have to deal with, enterricseptisimia of catfish ESC. It's very -- pretty much temperature related.

There's a temperature window when that bacteria will cause disease. So what the catfish farmers will do is pray for cool temperatures or very, very warm temperatures because it's outside that window.

Trout production in Idaho, for example, the water temperature is constant. It's just right for the growth of trout, fifty-eight degrees fahrenheit, but there are some pathogens that occur at that temperature, too.

And there's nothing we can do about that, other than look at vaccination, perhaps, and perhaps some antimicrobial treatments for the bacterial disease. So anyway, from a practical standpoint, it probably won't work.

It would really be great if we could do that but -- the other problem is, if you channel them into a hospital, terribly stressful for the fish, and that just exacerbates their disease problems and so it's a tough one.

MR. PRATER: I guess to try to, you know, derive some value from those points, though, I think -- and in the context

of pre-approval studies, part of the information that we generate has to do with pharmacokinetic parameters and if you can examine these parameters relative to what a therapeutic dose is and assuming that antimicrobial resistance occurs when you dose at subtherapeutic levels, then maybe you could determine in the pre-approval studies, what levels are actually present among the population and it could help us potentially in labeling a drug where we would ensure or rather minimize the number of fish that we're dosing subtherapeutically.

And I think some of that information can be collected in pre-approval studies as far as the individual pharmacokinetics, but if you examine them in context of the population, then they actually provide useful information about the population and what the percentage is of animals that you're dosing subtherapeutically. So that could be something that we could derive from pre-approval studies.

CHAIRMAN MacMILLAN: Fred Angulo made some suggestions which perhaps have some real merit on what we ought to -- what each group ought to focus on. The first item I think he mentioned was mutation rates in the laboratory. What are the thoughts about that?

Would that be an appropriate item for aquaculture, antibiotic drug companies to want to take a look at, or need to take a look at, or would that really be helpful for FDA and the Canadian equivalent in making a judgment about the relative

risk?

DR. REINSCHUESSA: Well I think, you know, if you determine your parameters for the in vitro studies appropriately, I think it can help. You're again faced with which bugs are you going to be using for your mutation rate. And, you know, obviously, I would assume that mutation, in terms of getting resistance, would be your ultimate goal there.

So that goes back to rate and extent, I think, of developing resistance and modeling that, I think, would be one of the very first basic steps to take. Are they just looking -- is he looking at mutation rate in general or is he looking at mutation to antimicrobial resistance?

CHAIRMAN MacMILLAN: I think his comment the enteric bacteria, but aquaculture's a bit different that way so I don't know. That's a good question. Maybe you ought to comment and then Wendy.

MS. OELLER: I wanted to dangerously digress a little bit that I don't think for most minor species indications, and I would include aquaculture, I think that when we talk about pre-approval studies, it's too late. Almost all of these drugs have been approved in other species. There are very few instances that we're talking about a new entity for a minor species.

And it seems to me that an unfair burden is being put on the minor species if they are the ones that are coming up

for approval now for things that have been out in the real world for thirty years to be said, okay, now you've got to figure out the mutation rate and you've got to figure out all of this other stuff, unless something is going to be done.

And I hate to even put these words in -- with the things that are already approved. Unless this responsibility is going to be shared -- I mean, if FDA is talking about going and removing all antimicrobials off the market unless they do this for every species, I really feel that we're being a little unfairly -- and I'm in an awkward position with one foot in the regulatory world and one foot in being advocate for producer groups.

But it seems to me that a lot of this stuff is random. If you're unlucky in your study and you have a terrible mutation happen in your very first petri dish, you could be unjustly judging a drug as dangerous that really isn't.

And the fact that a lot of these drugs, the majority of these drugs have been out in real world use in much larger numbers of animals and many different environments and unless there's been some red flag raised that it's incredibly dangerous, it seems a little bit strange to suddenly say we're going to go and not allow any drugs to be used in pheasants because it could be a threat to the public health.

So I have some questions about what information can

we use that already exists from real world use in terms of our baseline for supplemental things? I think if you were unfortunate enough to be sitting in the ruminant group where they're talking about new entities for feed lot cattle, it would be a lot more relevant; a lot more relevant.

DR. BUTLER: Those points are excellent. We could actually maybe move forward with some of those because, as Meg said, we are looking at drugs that have been out there forever, and so that, in terms of following the questions here, in trying to set out what would be useful -- and this is only a guess because we're not really sure, but for drugs that are already out there, there's more literature out there.

So if a sponsor of a drug is looking for pre-approval for something that's been out there forever can gather the information from X species, and to give Fred some credit, I don't think he was asking industry to sort of take a look at mutation rates specifically for each drug.

I think he was talking about gathering the information from all the pre-approval studies, that it would be a useful library of information. But I think if you're trying to get a drug approved, for example, you can take a drug that you know that tends to have a higher rate of mutagenicity to antimicrobial resistance for this and there's a cross reactivity, then you can take that information, pick a bug that is found commonly --

I'm just trying to say, you know, if I were trying to move a drug through, I'd say, okay, well, if it's catfish and salmonella's a concern and I'm going to use this drug, then I would want to put forward what I would like to get at this end is a study that has a control group of catfish in a controlled environment that is not too far off the normal housing conditions, put together the information that's known for other species and basing it on that, say, okay, we're going to guess that because this is happening or that is happening in other species, it may happen this way in fish, so that you're narrowing your focus.

Run it on a certain number of fish. Collect that bacteria back and take a look at the profile. Then you're just focusing it. And as you say, it's unfair to expect the one species to carry the can for everybody so I would expect, and I know that we'd be open to taking information from other species, taking a look at a pen full of the fish, treating them, seeing what the outcome is and matching it as much as possible to usual confinement conditions or if there are runways or if they're in ocean pens or whatever.

That would be a start, right? How are we doing here? Can you predict resistance development? Well, the literature is going to tell you what, for aquaculture, for the most part, whether or not there is resistance and then you can look at the profile in treating fish and say, well yeah, it follows the

profile; we don't have a worry. I'm just trying to --- one to five here.

DR. REINSCHUESSA: I guess, looking at already approved drugs versus not approved drugs is a differentiation we might want to make right up there and let -- but then again, because they are in water, I think that they are sort of -- you know, they're not pheasants and so there are some issues that are bit more important to look at in the fish.

But like, you know, why Tetracycline is allowed in a catfish and not in, you know, a red --- reared under similar conditions. Yeah, I agree.

MS. OELLER: And just one other follow on thought to that is, if we discourage approvals by making it too difficult, we're going to have fewer and fewer drugs in use and increase the likelihood of developing resistance, not only to the target pathogens but to others that are your innocent bystanders.

We're seeing that in lots of minor species because once one drug is approved, the pressure is sort of off everybody to get another one approved for such a small market. And American fowl --- and honeybees is now, after thirty years, becoming resistant to Oxytetracycline because it's the only thing they have.

And I think that we need to encourage having a broad arsenal so that we will not be constantly applying the same selective pressure.

DR. BUTLER: Yeah, that's real important. You need to have a few drugs so that there can be some switching through and because of the natural development of antimicrobial resistance with the one is an excellent example. So are we -- you moderator person, are we moving through your list? Have we got any substantive pieces?

CHAIRMAN MacMILLAN: We do, and why -- I don't know -- anybody want a break? They had scheduled a 3:30 break and so -- well, I didn't but the forces that be had scheduled a 3:30 break, so why don't we take a break and I'll collect my thoughts a little bit and maybe we can get through this. What time are we supposed to finish today? 5:30? Okay. Maybe a fifteen break. Will that work? All right, let's break. We'll meet back at quarter of four.

(Whereupon, a brief recess was taken.)

CHAIRMAN MacMILLAN: Okay. In terms of designing pre-approval studies, what I have so far is that the first step would be to look at the existing literature for unpublished information from a drug company's files perhaps on the prevalence of antibiotic resistance associated with that particular drug. Does that capture what we've talked about so far? I haven't even --

DR. BUTLER: The published literature.

CHAIRMAN MacMILLAN: Published literature, right. That would then give us some guidance or give FDA some guidance

about what the -- starting to give them some guidance on what the relative risk is.

It still doesn't predict what the -- or doesn't provide any, necessarily any data on what the risk to people is. That's still a separate issue, I think, but it's a start. So, as I went through the questions for consideration for the breakout, there seems to be a focus on modeling.

What factors should be considered when modeling resistance development in pathogen load. Can we make any progress on identifying perhaps a reasonable model that could be used in aquaculture?

DR. BUTLER: Did people agree that for various species, if you wanted to use the product in various species of fish, that you pick a representative bacterium for the species that's catfish. You want to use the drug in catfish, for example.

So you pick an organism that is commonly found, like a bacterium commonly found in that species and test a group of those fish with the drug having tested beforehand to see if there's an antimicrobial profile and then afterwards?

So you've looked at the literature, first of all, to see what is likely to happen with perhaps that bacterium in another species and that drug, that bacterium and the drug species, there's probably a combination in the literature.

Try it in a species of fish in a controlled

environment, checking the antimicrobial resistance profile before and after. And then you've got to -- you can say, yes, it's the same as what you expected and you understand that this particular antimicrobial resistance is not an issue. There did not turn up any cross resistance, which might happen, flipping from one species to another. That's it.

DR. FINEBLUM: I would like you to just please clarify what sort of bacteria you would select from. Would you -- would they be pathogenic bacteria or "commensal" bacteria that the fish will occasionally be infected with depending upon what's in the water?

DR. BUTLER: Well, from my druthers, I'd rather see something that is not a human pathogen. Although I said, for example -- well, no. A human pathogen or a fish pathogen, like salmonella, for example, I would prefer to see, not salmonella used in catfish but maybe that's the only one that can be counted on to be in catfish in a certain environment.

So if I had my choice, I would have picked a but that is an indigenous bacterium that is not known to cause any problem, either in the fish or in humans, and check it for its existing antimicrobial profile and then treat it and then check the profile afterwards.

DR. SIMMONS: What would you do with the data?

DR. BUTLER: That's a good question. This is -- I mean, this is new, isn't it? The AMR pre-approval, this is a

whole new ball game. Right? The question is, what do you do with the data?

DR. REINSCHUESSA: I think what I'd want to do is rather than trying to figure out what bug here is to decide if we'd like to try to at least suggest that some kind of a modeling system be done. Now, the question is, what do you do with the data?

From the kind of feeling I get from what people in other arenas are doing is, to some degree, this is an information gathering tool, almost, rather than necessarily a decision making process, unless you come up with something that is so out of the ordinary.

I mean, if you come up with extreme resistance showing up, then that would highlight, you know, maybe we have to take an action here. But it may be just a way of determining with ceratin reference bugs, and I don't know if it would be one bug per fish species or multiple bugs, but to at least have something to go on.

We have evaluated it in these and we feel that this model is what would happen in production and leave it at that for the moment. And then, if you start having surveillance issues, at least you have a baseline to it that you can compare to.

DR. SIMMONS: I'm wrestling with the question. To some extent, what you're talking about is already done

routinely. Let's say, feronculosis in salmon. You will go in, you'll collect the organism from the fish prior to treatment. You will collect the organism from the fish after treatment or from necropsied specimens, etcetera. You are going to do anabiograms before and after.

Whether you have adequate numbers to make any distinguishing decisions or patterns from that is another question, but I think that's pretty standard in any species you're going to go. You're going to do pre and post treatment antibiotic monitoring.

Actually, you know, we -- it's truly designed to look at really what you're doing in regard to efficacy. But it would certainly pick up, you know, if you had a massive change, everything went resistant, then as a sponsor I would be questioning whether I want to move forward with that agent in that species.

DR. REINSCHUESSA: That's for the target.

DR. SIMMONS: That's for the target pathogen. The question here is much of what Fred mentioned early on is routinely done, but in the target pathogens.

DR. REINSCHUESSA: With antimicrobial ---

DR. SIMMONS: What we would normally do in this is, whether it's done pre-approval is another question but mutation frequency, that's -- again, this is not something that comes up as often in the U.S. but it certainly comes up in other

markets.

Mechanism of action and mechanism of resistance, we would normally put together a risk assessment that would go into those and also detail how resistance for what we would know would develop, if it is known pre-approval.

In many cases, these things evolve over time and so, my concern here is, how much of this information would be pre-approval? If it's like we say, that this is the last species to be developed after four other species have already been approved, and you may have that information.

The biggest issue I'm wrestling with is not -- I'm not trying to say we don't want to provide information. What I'm saying is, what type of information is meaningful and we can make a decision versus if it is just information for the purpose of having it, why should it be pre-approval?

And that's the issue I'm wrestling with is, if there is meaningful data that we can provide that we're happy to do so. I'm having a hard time with this and it, to me, still falls back to the classification of the antibiotic one, two or three.

If it is a fluoroquinolone, then you're going to want some very specific information about the potential risk for that. If it's an antimicrobial agent that is not widely used or has a very minimal role in human medicine, then the degree of information and type of data you're going to request would

be significantly different. And that's what I'm wrestling with.

DR. BUTLER: So you are doing antimicrobial resistance profiles, pre-approval already?

DR. SIMMONS: When you do a efficacy study, you collect the organism and you would look at the sensitivity pattern for a number of antibiotics, including --

DR. BUTLER: Sensitivity ---

DR. SIMMONS: Including the organism for -- or the antibiotic you're developing as well as the competitor's. And then you would also measure that in any samples you've got post-treatment.

DR. BUTLER: Right.

DR. SIMMONS: And that's --

DR. BUTLER: Well, sensitivity is quite different from the antimicrobial resistance profile and whether or not it has the ability to a susceptibility test, gives you quite different information than you would get on an antimicrobial resistance profile, saying that it's capable of transmitting antimicrobial resistance --- so susceptibility testing is quite different from antimicrobial resistance profiling.

DR. SIMMONS: Well, you're talking about mechanistic versus the standard MIC type work. I agree, yes, it's quite different. And I'm not aware of anyone that would be routinely developing that type of information.

DR. BUTLER: I think that's what we're looking for but that's my understanding. That's what I thought we were looking for, tools and recommendations to profile --- predict antimicrobial resistance.

And if it's an old drug and incredibly in some species of fish, it turns up a cross resistance pattern, then that would be a problem. But it couldn't happen because of the difference in fish species. So that would be what I'm suggesting, not naming a specific bug.

Can you hear me okay? Not naming a specific bug but -- she said she can hear me, so -- not naming a specific bug but --- a model where you do this test so it will fit nicely into the profiles that you're doing already, but simply would be adding the antimicrobial resistance profile which is what Frank would like to have his library --- what's the frequency of this, of mutation or what is the -- what are the tendencies in terms of antimicrobial resistance mechanisms.

So this fits into your profile already, is my understanding, except adding that piece for antimicrobial resistance.

DR. SIMMONS: I don't know what it is you want --- I still don't grasp what it is you want ---

DR. BUTLER: Well, specifically, the methodologies are for the people who listed them the other day. Here are five or six different ways you can transfer antimicrobial

resistance, whether it's a plasmid or it's a tendency for a gene mutation to happen under pressure of an antimicrobial.

So there are five different methods and what we want to know is, what are the chances, using that antibiotic on that species of fish in those conditions, that antimicrobial resistance will happen.

You can do -- I suppose you could do a mathematical model, but it wouldn't be as valuable as incorporating it into the current model where you indeed have to give all of that information on the pre-approval for a drug, and just adding that step, taking a look at the bacteria beforehand. I'm not talking susceptibility testing. That's quite a different issue.

CHAIRMAN MacMILLAN: So, just to play the devil's advocate, if you find that there is a plasmid that transfers resistance, what do you do with that information?

DR. BUTLER: Well, that's what a regulatory organization needs to know, so then that bacterium, which is indigenous to fish, presumably, can transfer that to a human by simply -- if I'm picking up a fish to prepare it in a kitchen and that bacterium, which maybe doesn't want to live in or on me anywhere, in that short period of time can say hi to the enterococci because I just ate the piece in the salad I was preparing while I was handing the fish and transfer that antimicrobial resistance into my enterococci.

So then, three months later, when I get pneumonia, the number one drug is not as likely to happen, as I say, --- drugs but it certainly can't -- Eryrothmycin --- can happen. Anyway, that's the process I'm talking about. That's why you need the antimicrobial resistance profile information beforehand.

CHAIRMAN MacMILLAN: But again, playing the devil's advocate, how do you know that that's going to be transferred to your enterococci?

DR. BUTLER: That model that I described has been described well in the literature, where there's transfer of antimicrobial resistance. That's the whole point. It's not the bug from the fish that's a problem. It's the bug from the fish transferring its antimicrobial resistance to my bugs through whatever mechanism.

CHAIRMAN MacMILLAN: And I apologize, I'm not familiar with that model or that part of the literature, but have they -- they've identified the probability of that happening?

DR. BUTLER: I don't know what the probabilities are -- yes, the process has happened. Yes, that has happened. That's the point. As I say, the fish bacteria --

CHAIRMAN MacMILLAN: There's no difference in fish bacteria from any other bacteria --

DR. BUTLER: Right.

CHAIRMAN MacMILLAN: -- in many respects.

DR. BUTLER: Especially if they like a certain temperature and pH which is different in a fish for me. So basically, when they come to me and they contact me, they don't live in or on me for too long, so the transfer of antimicrobial resistance, that's a problem.

CHAIRMAN MacMILLAN: Right. But I'm still wrestling, myself, with what's the probability of that happening, because it seems to me that if you find a plasmid in a fish in aquatic bacteria, it has resistance to whatever. What's the probability of that being transferred to you?

And I don't know that there's any model -- I know biologically it can happen. But if I was a regulatory agent, I would want to know what's the relative risk of that indeed being transferred to you and I don't know that.

DR. BUTLER: Well, it certainly happens and I guess this is where I usually say there are far too many microbiologists and not enough veterinarians. In this case, I think we have a dearth of microbiologists who could address that, because my colleague who works with me in Ottawa, for example, would say, oh no, this happens, this step, this step, this step, and the --- whether or not he could address the risk of real numbers, I don't know.

I think that's basically the exercise in December was with respect to the risk of antimicrobial resistance with

campylobacter in chickens. So I can't speak to the numbers but that's what we're here for, is the transmission from one to the other. It's not seeking the fish bug, then, to me. Right?

CHAIRMAN MacMILLAN: Well, there's been some reports -- I identified one yesterday morning from the UK, a couple of scientists there that did a qualitative risk analysis about that very issue. And for what it's worth, their conclusion was that the probability of that happening was very low. And so, I'm just --

DR. BUTLER: The qualitative as opposed to quantitative?

CHAIRMAN MacMILLAN: Correct. It's very -- what I'm getting is it's very, very difficult to quantitate.

DR. BUTLER: So that's what a risk analysis is. Right?

CHAIRMAN MacMILLAN: Well, there's a quantitative and there's a qualitative risk analysis. But there's, for pre-approval study to be helpful in whatever we design or whatever we propose to FDA, it seems to me, somehow or other, we need to keep that in focus and develop something that's going to give the decision maker that degree of probability of -- or that degree of risk so they can say, well, it's a fifty percent chance or it's only a ten percent or one percent chance.

I don't know how to do that. I don't know that the -- and I apologize. I haven't seen the model that you refer to

that would give me any type of support that way, for making a decision.

DR. BUTLER: Well, if I could say, the front to back piece has not been done. That's part of the problem with the whole antimicrobial resistance, and the piece that I told you about has been shown in each step what happened. To go from the fish to the person to the pneumonia in the hospital, that piece has only been connected by inference and that's where the good science -- it comes to a point where you have to make a decision --- all the information in some cases.

Well, unfortunately, as a regulator, there comes a point when the science comes together enough that you have to make a decision in the interest of public health without complete science. We've had incidences in Canada where people made some bad decisions, saying no, we don't have all the science.

So, if I sound -- I mean, it's not just me. The reason this whole issue is being brought forward is because the science, the wealth of the science is saying, yes, there's an issue.

So, what I described to you is one of the mechanisms. We're talking about trying to find a model in aquaculture. I think this is -- the species that would be the easiest in terms of the most background information because they're not new drugs. Well, they're new drugs to fish.

So, I'd say this would be easy one except for the implications in the environment and that makes it very, very complex. But in terms of putting forward a model on antimicrobial resistance, the one I suggested, I'm just putting it forward as a suggestion. Put them in a confined environment. You do this.

This is an in vivo study. You could do an in vitro study but I think, you know, from what I can see or what I've learned or in following --- issue, the in vitro situation, or in vivo situation is the nearest what happens out there in industry is probably the best. So, I'm just putting it forward. I'm not passing the stone here, but, what are the other models?

DR. REINSCHUESSA: Well, I guess what I'm hearing here is that we're trying to figure out how the studies would be used by FDA if you find out the method -- the speed of resistance developing and the type, which is what you haven't been looking at, is what kind of resistance pattern would be developing then -- i.e., is it plasmid? Is it a DNA shift or whatever?

Now some of that might be more frequently associated with certain drugs. So again, you can probably use mammalian counterparts for that, because you say, well, this is generally not a plasmid mediative thing but certainly integrons and things like that; maybe not.

But I guess you could take the bugs and co-culture them with some kind of human gut to -- gut flora to see if it transfers --

DR. BUTLER: That would be another model, too. ---

(Comment away from microphone.)

DR. REINSCHUESSA: And that's where picking the model organism comes in again and that's where we need a whole session just on that. I have trouble, too, with the what are we going to do with the data and to some degree, I think it's valuable to create a database.

But, like you say, we need to know where we're going before we try to model how we're going to get there. So what factors should we consider when modeling resistance? I don't know. I don't know.

MS. OELLER: I think that we need to approach this from a couple of different scenarios. I think that the point of having breakout groups is to deal with the issue that affect the individual producer groups. I think that since we're talking about aquaculture, we're talking almost exclusively about anti -- when we talk about antibacterial, we're not talking about new entities.

And I think that we need to make that clear when we go back and report to everyone else that we don't think that all of these studies that they're talking about for a new entity should be applied to a supplemental approval.

If they want to get into, you know, complete profiling of a new entity, I think that's fine, but I think it's going to affect this group very little. I think that what we should be suggesting is that we don't have to do any of that, but what we do have to do is study anything that's different that would be different pathogen, different target pathogens and their resistance development.

I think that CVM has made a call that antimicrobial resistance is a human food safety issue, but I think in aquaculture, we need to point out that it's a lot more an environmental issue.

And I think that we should probably be proposing some kind of a baseline that will be used then for post-approval monitoring in terms of resistance levels and I think we should be proposing some kind of a risk analysis based on environmental exposure for different kinds of species and different kinds of indications.

MS. OELLER: I think that the sponsor can at least provide us with the data of where it's likely to be used, like this is going to be used in catfish ponds or this is going to be used in raceways or all of the above or net pens.

This kind of -- I mean, if we get all of the factors of where it's going to be used and what kind of bugs it's going to be used against, either they can do a risk assessment or FDA can do it. I don't have a strong feeling.

(Participants away from microphones.)

MS. OELLER: I'm open minded about that.

(Laughter.)

MS. OELLER: I don't know. It just seems to me that we're dwelling on all of Dr. Angulo's questions as if these were brand new things that no one had ever seen before and I don't think it's appropriate and I think we should get out of that business and let the other breakout groups worry about that, unless we're talking about a new entity.

DR. FINEBLUM: I think that several good points have been raised. One of them is that, there is always going to be a risk and what we want to do is try and minimize the risk. And these techniques of risk assessment/risk analysis have been brought up and I think that they can be extremely useful because what they're going to do is try and help us figure out which components of the pathway, you know, from start of raising the fish all the way through to consumption and environmental exposure, all the various possibilities for exposure of a person to some form of antimicrobial resistance because of the use of the antimicrobials.

If you can create that pathway, and then figure out -- the pathway can be huge and extremely complicated. I think that's another difficulty here, is that we're kind of drowning and it wasn't intended in all of these various factors and we're sort of overwhelmed.

If you can make models and then do what's called a step-wise process -- I heard a presentation recently by someone from a Dutch company in which they are proposing a step-wise or iterative process of doing risk assessment where your first pass is qualitative.

You are coming up with just very basic ideas of what is the relative risk at each step along the way within your model. And based upon that, you focus -- you choose which parts of your risk assessment that you want to focus on because we don't have all the time in the world. We don't have all the resources in the world.

And then, based upon that, then you might to a quantitative but deterministic or point estimate focus on that aspect of your model. And depending upon which of those are most -- seem to be most critical in determining resistance, then you can do a quantitative which is going to be much more labor intensive.

But meanwhile, it would probably give you the results that would be most relevant and most useful. So it may be best to kind of step back and try and think, okay, you know, what could go on and I'm trying to sort of clean out the big picture, and then focus on, you know, what are the relative risks of this particular thing happening.

And if you think this relative risk is large, well then, let's look into that area more closely. That may be

easier than just kind of trying to deal with it all at once with equal depth and effort in all aspects of it because that seems to me to be --

DR. BUTLER: I think a risk assessment is a good idea, although it is an additional burden, whether it be to industry or to the regulator to take a look at that, but I think it has to be done at some point.

I agree, also very much with what Meg was saying about -- and reiterating the point about we're using old drugs and it's whatever. Although, the caveat here with respect to antimicrobial resistance is at least taking a look at the background literature to say what is the risk? What is the usual mechanism?

I mean, whatever our -- the bug is that I suggested in the earlier model. But it still has to be looked at. AMR still has to be looked at, just as for every species when we approve drugs. We have to go species by species. We can't say, just because it works in those animals or just because the AMR profile is that way in those species.

I would contend that we'd also want to know which way it's going to go in fish, not every bug that comes along but at least one, some sort of indicator bug, whether it's a commensal, just an indigenous bug in whatever the species of fish is.

I think we're looking for that confirmation that it

follows what everybody else did and it would be a little easier -- as I say, it would fit already into what you're doing but instead of culturing sensitivity type of thing, you do an antimicrobial resistance profile and I'd say, probably 99 times, if we were guessing risk, 99 times out of 100, what happens in fish is going to be what happened in cattle and sheep and every other species.

But the piece, the added piece here is the AMR piece to say, what is the propensity? What is the risk? And it's likely to follow the others and it'll be fine. But because it is in other species, the nature of the drug approval process is we have to say yes in that other species which, granted, is kept in a very different way than our terrestrial species.

DR. REINSCHUESSA: You're sort of grouping fish as a species.

DR. BUTLER: Yeah, I know.

DR. REINSCHUESSA: And for us, you know, there are species --

DR. BUTLER: I'm speaking in the general sense.

DR. REINSCHUESSA: Yeah.

(Participants away from microphones.)

DR. BUTLER: --- in every species for approval ---

DR. REINSCHUESSA: I mean, I would hope that with some work in the next ten years, we'd be able to group some of the species together, at least based on PK studies. But we

might also have to be grouping in terms of their microorganisms as well. I don't know. Maybe at least in their environmental cultures -- culturing practice, not cultures.

(Laughter.)

DR. REINSCHUESSA: Do we want to move on?

DR. SIMMONS: The difficulty I was having, still, going back to, you know -- it's almost like, well, just grab these fish, grab this bug, throw it in, do your profiling on that and I think Dr. White and Dr. Cray gave us a very good example of the magnitude of the issues associated with it.

So, not only study design but interpretation of the results. It's very routine procedures to take organisms at just below the MIC, pull them out, see what you can do in the way of inducing resistance.

These type of things are very difficult to interpret and that's what I'm struggling with is, again, on a pre-approval basis, I don't see a simplistic answer and I always will go back to the classification of the antibiotic and, you know, what is its importance in human medicine.

That would drive the next step, but I'm very much concerned that there's no real easy box we can put it in or we can't say, that's the model; that's what we want to do.

(Participants away from microphones.)

DR. BUTLER: Well, I think you have to put forward

several --- suggest, because that's what they're asking for and we're not going to come up with an answer today, although I think this is an opportunity for industry and the public, although --- the public are here, to come forward with a suggestion.

I mean, I'm not speaking here as the health candidate person. I'm speaking of someone interested in coming to a solution in the antimicrobial resistance area. So, I don't have any -- I don't have an answer --- upon this suggested model.

What I'm trying to say is, let's get it into what you're doing already. Let's come forward with a suggestion because we're here because AMR is a problem and that some of the people who are gone now were saying, what I see down the road is people saying, bang, and not using drugs in animals because we don't want it there.

It's going to cause this; it's going to cause that. So, we have the option, today, thanks to the FDA, of putting forward some models. I'm not suggesting you're right, but that's what our task is in this breakout group. We could say, well, we just think it's too big of a problem.

There were too many questions asked and we can't think of anything but so be it. I mean, if that's the consensus of the group. So I'm just suggesting these are possibilities and it actually does fit into the --- methodology

and although the AMR assessment is an extensive addition, it's true.

CHAIRMAN MacMILLAN: What if the innocent bystander issue were addressed in post-approval monitoring?

DR. BUTLER: My regulator hat goes on as soon as you say that. Why did not we identify that beforehand? If we knew that antimicrobial resistance was a problem -- I think it's going to be the least problem in aquaculture because of the use of drugs that have been around.

But if you ask me about, if it turns up in the post-approval monitoring, why didn't we ask that first because we know that happens? So that's when the regulator hat goes on. So, if we can identify beforehand the public of interest in our doing that ---

DR. REINSCHUESSA: I think one of the things I worry about, just looking at the human classification of the drugs is that, you know, because even like for Tetracycline, you can co-select so many other drugs that, just relying on the fact that they are low importance in human medicine may not be a real valid way to go. I don't know.

If we're trying to figure out what the patterns are in real bugs and we can make a case that with the models that at least we're not seeing massive multi-drug resistance develop rapidly, then I think you have something to stand on.

If you find that that happens, then that's something

to warn you about the drugs. But you, you know, you may have some co-selection or co-resistance development that you wouldn't know about if you just say, well, it's a drug that we don't deem that important for human medicine.

And unfortunately, that goes for a lot of the --- and disinfectants and that's not going to be an easy issue to deal with, too, because, I mean, if you're worried about chlorox, it's just going to be a big problem.

CHAIRMAN MacMILLAN: Renata?

DR. REINSCHUESSA: Yes.

CHAIRMAN MacMILLAN: If somebody wanted to get oxytetracycline approved for an aquaculture species now, or Meg or Joan, what are the prospects of getting that done, given what we know historically about oxytetracycline, given that oxytetracycline is used in orchards.

It used to be used to treat shoes so that they wouldn't smell and, you know, it's just been widely, widely used. What kinds of -- and we have an awful lot of information about plasmids and all related to oxytetracycline. What are the prospects of -- what steps would we go through and what are the prospects of getting that approved now?

(Participants away from microphones.)

MS. OELLER: But the initial question is, what about the two that we already have approved for use in at least some aquaculture species, either selmonids or catfish or lobsters?

Will we go back to square one and require, you know, a model for those as well when we do approve, you know, another indication for oxytet?

And I'll tell you, I believe this is problematic right now. I don't think that if we put one forward it would be clear sailing within CVM.

DR. BUTLER: I think any antibacterial that goes forward --- until the antimicrobial resistance --- decide --- are going to be --- which is why we're here today, to make these recommendations.

CHAIRMAN MacMILLAN: Well, I am just trying to get some sense of where scientific regulatory people, how you would -- what the prospects would be because we don't know what the innocent bystander risk is. It's there. We've known that's there for a long time. We still don't have a measure of the risk and what the probability of that shift or that transfer occurred.

And I don't, from a scientific standpoint, understand how we could ever measure that risk. And so, yeah, it's going to be a guess, and I understand the need to have some sort of measure, but I --

DR. BUTLER: But it's not at the point of guess anymore. When we know that this happens, we can do these assessments. You make some judgments, step-by-step, exactly, but you can.

It's gone beyond the we can't prove the point. Truly, it's gotten to the point where we're asking for recommendations. Now I don't -- you guys can speak to which way the FDA is going to go after this, but I'm guessing it's going to be we do have to do --- does have to do a risk assessment, take all the information and then say fine, for any antimicrobial to be passed in the future, you have to do this, this and this.

So it's not a guess anymore at all. And yes, it's a complex scientific point, but it's not a guess. It is based upon this science and step-by-step. It isn't the best estimation but it's still a good estimation, going from one end to the other, and it can't be denied any longer.

You said we've known for a long time and as a -- well, being a Canadian, we've had things that --- inquiries that -- these government inquiries that call people in and say, when did you know that was a problem?

And people say, well yeah, I knew about it five years ago. Well, what did you do about it then? So, this is basically what's happening in antimicrobial resistance. You've known about it. Now there are tools to assess with and --

CHAIRMAN MacMILLAN: Yeah, well, I would say we've known that biologically this can happen. We've not known if it's a problem. Okay? There is a difference. And in the fish literature, in the 1970s, you could identify plasmids in fish

pathogens that could move from one fish pathogen to another or to aquatic bacteria.

DR. BUTLER: Right.

CHAIRMAN MacMILLAN: So you can put two and two together and figure, well, it could happen to a human pathogen. But I don't know that we have -- you say we have some information that takes it out of the realm of quantitative and I still struggle with that. I don't know what that quantitative measure is.

DR. BUTLER: I wish I could solve it for you but I'm -- and I know Fred is pretty strong on this stuff, but there is data in CDC about -- on a human side about the tremendous rise and I worked at Canada's CDC before I was where I am, so that's where I got a taste of antimicrobial resistance problems with tuberculosis and BRE and, oh, you know the list. The list gets longer and bigger, more bacteria, more cases of death, so that's what the push is. There's no question that you knew that piece, and I don't think we knew in the '70s that it could take that track to humans.

And whether it's a real or a proceed with at the end where we have this huge list of resistant antibiotics, a risk that's a perceived risk to the public is a risk. And as they say, no, you can't have the drugs anymore, because all those people over there are dying from tuberculosis because of multi-drug resistance. I mean, I'm not -- I'm just stating -- I'm

being the devil's advocate.

CHAIRMAN MacMILLAN: Sure. No, no. Well --

DR. BUTLER: I'm not a microbiologist who says, here is whatever. I just know the big evidence piece is there and that's what the crunch is coming to because in the '70s we knew those things. In the '70s, we couldn't have this discussion, but we're now in the 2000s and we know that these things can happen and so, what are doing in public health about it?

CHAIRMAN MacMILLAN: Right. You know, we challenged Fred, Fred Angulo --

DR. BUTLER: Oh, yes.

CHAIRMAN MacMILLAN: -- to provide some data. He couldn't do it.

DR. BUTLER: Well, you mean from fish to people?

CHAIRMAN MacMILLAN: We challenged him --

DR. BUTLER: I'd say that --

CHAIRMAN MacMILLAN: We challenged him to provide some information that would support his contention about aquaculture being a public health --

DR. BUTLER: Right.

CHAIRMAN MacMILLAN: -- risk to people.

DR. BUTLER: Right.

CHAIRMAN MacMILLAN: And the evidence he was able to provide --

DR. BUTLER: Was all human.

CHAIRMAN MacMILLAN: No. It was all very, very, very weak, and I'm not -- you know, I don't want to demean Fred or anything. It's just a reflection on the information that's out there.

And so, what I struggle with, and perhaps others, is how do you quantitate -- how do you give a regulatory agency, the people that have to decide, one way or the other, some substance to make a judgment? Do you always -- because it sounds like FDA has said, all right, we are going to accept some risk.

We haven't decided what level of risk we're ultimately going to accept, but we are going to accept some risk. So once they get to that decision of what level of risk they're going to accept, we will watch the risk of going from a bird or a fish to a human.

And I -- you know, in terms of designing a pre-approval protocol now, I do struggle with what are going to do with whatever information you get? And so, with that in mind, whatever we recommend ought to be very clear in what we're going to do with the data.

I think it's grossly unfair to ask a drug company to go out and test a representative, a commensal bacteria, to see if the antibiotic will induce resistance or there are cassettes of resistant DNA there and then make the jump from that commensal having the resistance to it impacting people, and

that's just what I struggle with. And I'm really sorry --

DR. BUTLER: No, I understand.

DR. REINSCHUESSA: And that's where I'm not sure we can make that jump but I would think that possibly you could use that commensal then in your post-market surveillance. And if you can use something like that as a tool, what I guess I would say is, what suggestions would industry have as far as trying to understand what risks there are from it.

I mean, have you any suggestions to go beyond the kind of studies that you've had where you're looking at your susceptibility patterns in the targets, and not just for fish. I mean, is there some way as you would, as a concerned parent worrying about your kids getting resistant bugs, where you would say this would be a good way to address this issue?

DR. SIMMONS: The first thing that comes to mind on this, but I've even struggled with that, is that you put together an effective dose regime. Whether it's a concentration dependent or a time dependent antibiotic, you're going to work from that.

The reason I struggle with even that, and that's why I decided I don't know enough microbiology, especially after listening today, that there are so many variables that can confound the validity of what you've generated.

Even if let's say I've got a concentration dependent antimicrobial agent and so I'm going to hit it very hard, very

high. I'm going to be a ten to fifteen X, the MIC, well, eventually you're going to be down below the MIC and I'm measuring serum levels. What's going on in the gut?

So even doing that, I may not be doing, you know, knowledgeable; but from our viewpoint, number one, we will know how the antibiotic works. And when you know that, you know what the resistance mechanisms -- I'll jump out of our area and go to somebody else.

Let's say Amoxicillin, we want to develop Amoxicillin for fish. Well, it's obviously going to work on the bacteria cell wall. What are the resistance mechanisms, their betalacatmeses, constitutive or inducible, gram negative, gram positive?

So you'll take a look at that so we know that, but if I do a study that shows, yes, I induced betalactamese and even when I induced betalactamese, it might protect an organism that can't produce betalactamase. I still have difficulty knowing how I interpret those results. And that's what I'm really struggling with.

Now, one thing that is happening is, you've got CECA in Europe. You've got NARMS; you've got other programs. These are maybe after the fact. I don't know how you want to classify it. And we generate our own global surveillance data where we're measuring, you know, antimicrobial sensitivity patterns and this is based on MICs.

So if you begin to see a shift, you can tell something is happening, but we're not doing that for organisms other than the target pathogens. So again, I don't know if we're generating data that's going to be valuable from the other arenas.

DR. REINSCHUESSA: Do you think it's worth looking at --- especially in terms of environmental use where you feel --- where they're spraying the trees or ---

DR. SIMMONS: That's a tough one to answer because, you know, unless you develop that into an overall surveillance program, and then what do you --

DR. REINSCHUESSA: That's just part of your whole profile of where are we going with --- and what do we have to do to mitigate? Possibly your nontargets might give you even a better indication of how to counter the next step. I mean, it might have a market advantage. I don't know.

DR. SIMMONS: I don't know the answer to it. That may be an avenue. I just can't answer that one.

DR. BUTLER: So there is a dearth of microbiologists here.

CHAIRMAN MacMILLAN: Well, it certainly is a bit of an intellectual challenge. We in aquaculture would want to be able to make sure the drug company can provide the data that's needed for people to make a judgment. And ever since all this issue came up, I have struggled with how do you actually do

that?

I can provide some objective measure, imperfect, but how do you provide some objective measure of what the real risk is? And because there are so many steps involved in order to get to the human side of things, it's really difficult. And I don't know how to address it.

I'm trying to think of something we could do this after in whatever time we have left to make some progress in addressing the pre-approval study expectations. And I'm really open to suggestions that way. I would assume -- are the terrestrial animal folks probably having the same difficulty?

DR. BUTLER: I would say in spades, if you're a card player, yeah, because I'm dealing with drugs like fluoroquinolones -- so yeah, they have bigger problems than aquaculture.

CHAIRMAN MacMILLAN: So what if -- if you do post-approval studies, and I'm naive about this stuff, if you do post-approval monitoring and you find that salmonella is developing, it's infective to people causing mortality and morbidity, and it's resistant to fluoroquinolones, what's the action? Does FDA or Canada folks, do they say, all right, no more fluoroquinolones in people -- or in animals?

DR. BUTLER: You're not allowed to ask about Canada yet. We're still in the same process. That's why we're here learning about the U.S. I'm not really sure what the U.S. is

doing there yet either.

CHAIRMAN MacMILLAN: Okay. So what would FDA do, then? If you find that fluoroquinolones -- I guess it's used in poultry.

DR. BUTLER: And cattle.

CHAIRMAN MacMILLAN: And who?

DR. BUTLER: Cattle.

CHAIRMAN MacMILLAN: Cattle. Okay. Well, I know it's at least used in poultry. It's in the water; right? So you find that poultry campylobacter are developing -- is it used to treat campylobacter in poultry?

DR. BUTLER: They try --

(Simultaneous conversation.)

CHAIRMAN MacMILLAN: Okay. Well, campylobacter is there.

DR. BUTLER: Right.

CHAIRMAN MacMILLAN: Campylobacter is there as a salmonella. So you find that salmonella is developing resistance to fluoroquinolones and --

DR. BUTLER: That it's a reality.

CHAIRMAN MacMILLAN: So what's -- it's a reality?

DR. BUTLER: You call meetings like this to talk about antimicrobial resistance. That's what happens when you find those things out.

CHAIRMAN MacMILLAN: Okay. But what does the agency

then do? Is that what you're struggling with, what do we do? Do we stop it?

DR. BUTLER: Absolutely on the nail.

DR. REINSCHUESSA: At the moment, I don't know if there's a legal method as in public --- drugs.

CHAIRMAN MacMILLAN: Imminent hazard.

DR. REINSCHUESSA: Well, there is imminent hazard, but is antimicrobial resistance an imminent hazard?

DR. BUTLER: That is exactly --

DR. REINSCHUESSA: It takes a long time to --- I mean, even with imminent hazard you might ---

DR. BUTLER: It's only so imminent. That's the same as with Canada. Is it a hazard? Well, the literature is suggesting, and absolutely when salmonella is developing these kind of resistances, it's a serious issue and so the decision has to be made -- the discussion has to take place which is why there are meetings like this.

And so, what do you do? That's exactly the question. We're not sure -- I'm going to speak for Canada so these guys don't have to. We're not sure what to do at this point so we're looking to other jurisdictions, and I'm sure that the FDA is doing the same thing to see what other jurisdictions are doing with this.

For example, is it the Danes -- our fellow from the Netherlands could say, the Danes, the pork producers, took it

in hand and they were the leaders in using antimicrobials for growth promotion. The producers decided themselves, thank you very much, that we're just going to start easing out of this business.

So that makes it a lot easier for the regulator, she said, hinting loudly, if industry decides to take this into their own hands and say, okay, we're going to just limit ourselves to this, that and the other thing. That means they still have the big guns in their back pocket for therapeutic use.

And then regulators don't have to bring down the hammer that we don't like to do; we're not sure when to bring down the hammer, and it takes five years to bring down the hammer anyway, same thing with us. So you have to have a discussion, a public meeting, and that's what this is.

DR. REINSCHUESSA: And I think outside the box is a really good --- of rather than having an adversarial industry --

DR. BUTLER: Absolutely.

DR. REINSCHUESSA: Possibly industry can help self regulate somewhat or prudent use guidelines --- used.

DR. BUTLER: Yeah.

CHAIRMAN MacMILLAN: But here you've got salmonella that's resistant to tetracyclines. Worldwide, tetracyclines are still very widely used.

DR. BUTLER: But they're not as widely used in human medicine as fluoroquinolones which are essential; right?

CHAIRMAN MacMILLAN: Okay. So that's the dividing line, then, is that --

DR. BUTLER: Yeah. That's what they used in human medicine that worries people.

CHAIRMAN MacMILLAN: Okay. And so that's where the Framework document comes into play -- where do you put the drug? Is it one, two or three?

DR. BUTLER: Yes.

CHAIRMAN MacMILLAN: Okay. So we made some progress. We need to know if we're going to put it in a one, two or three class.

DR. BUTLER: We want you guys to lead. Go.

CHAIRMAN MacMILLAN: Okay. But right now there is no mechanism, really, other than imminent hazard and that sounds controversial to -- the reason I asked that question was to get a post-market monitoring as a way to try to address innocent bystander issues.

In other words, the proposal would be, what if you do all these studies as Meg was suggesting and which is largely a review of the literature and stuff like that, and you do all the other approval process that you currently have and then you say, all right, we're going to go to -- we're going to maybe even provisionally or conditionally approve or approve it, or

we're going to have a good monitoring program in place to track the prevalence of resistance to this agent amongst bacteria that might be -- might occur around people.

DR. BUTLER: That's going on --- post-marketing ---

DR. REINSCHUESSA: In fish.

DR. BUTLER: In every other species, so if you're looking for that to be the answer, it's my understanding that in all the other species, basically, that is happening and if we don't -- I just --

DR. REINSCHUESSA: I think it's happening for selective pathogen in selective spots like water --- versus necessarily in the environment.

CHAIRMAN MacMILLAN: So it's going on like -- is it going on for salmonella? I know FDA does a salmonella survey but the literature I got from FDA didn't suggest they are doing sensitivities. They are doing --

DR. REINSCHUESSA: You mean the one from the fish?

CHAIRMAN MacMILLAN: Yeah.

DR. REINSCHUESSA: Yeah. I can ---

CHAIRMAN MacMILLAN: Okay. See, that's not -- the presence of absence of an antibiotic resistance organism on the fish is one thing. We're talking about moving the resistance factors from aquatic bacteria to human bacteria and not necessarily salmonella. But it goes from -- I don't know -- we've got staff epidermitus on our skin. Do people get disease

from staff epidermis?

DR. REINSCHUESSA: Yes, you can.

CHAIRMAN MacMILLAN: Okay. So that's a good example. All right. So it goes from the aquatic environment to staff epidermitus through several steps. How are we going to be able to tell that that resistant staff epidermitus came from the aquatic environment?

DR. REINSCHUESSA: Some of the --- and actually when we start then cloning the genes and sequencing, you'll find real specific --- sort of what Dave White was showing you that. And you can say that -- no, I don't know if you can say it came from here or there or from here to that, but at least you can say there's some kind of likelihood that these guys transfer between each other.

CHAIRMAN MacMILLAN: Well, you know, it's an interesting idea and I can see where it could work. On the other hand, there is recent literature that identified -- wish I had a better memory but in apple orchards, the same DNA pattern for resistance in whatever bacteria they were looking at, in the apple orchards that have been treated with tetracyclines, that was in fish, fish bacteria, so which came first or did they arrive independently? I don't know. But it makes it difficult to use that as your marker.

DR. REINSCHUESSA: Oh, yeah. No, I agree with you because like, just like I was saying with the hog run off goes

into the water and it could be the antimicrobial use that caused the bugs in the fish, you know.

CHAIRMAN MacMILLAN: So what you get into, then, if it occurs, if staff epidermitus --

DR. REINSCHUESSA: And it came --- it could go from people to people.

CHAIRMAN MacMILLAN: Sure. So if it came that way, then do you go out and stop the use of tetracyclines in minor animal species?

DR. BUTLER: Maybe in all species. I think the public, when they start understanding this issue is going to say, forget all of that. That's my worry. You can do a lot of fingerprinting to track it down to the species or the treatment and they're getting better and better at doing that tracking. But I'm worried that the hammer comes down, saying, forget the antibiotics --- now, I can't see them saying no to therapeutic use but for salmonella ---

CHAIRMAN MacMILLAN: Well unless you're with PETA.

DR. BUTLER: Yeah.

(Laughter.)

CHAIRMAN MacMILLAN: PETA people wouldn't put animals at the top.

DR. BUTLER: Yeah.

CHAIRMAN MacMILLAN: Well then, and then the funny thing is, we ban all animal use and in terms of human health,

public health, it will make --- difference.

DR. BUTLER: It depends on cross resistance. I don't know what cross resistance --- and it depends on what new therapeutic agents come along because tetracycline could in fact be --- if something comes along that can cure multi-drug resistant tuberculosis and for some bizarre reason, tetracycline causes cross resistance to that new drug, which can save a million --- people ---

CHAIRMAN MacMILLAN: It could happen. The probability is probably pretty low and the other thing that comes to mind, though, is that some of the data presented today and perhaps yesterday was that it takes a long time to reverse the prevalence of antibiotic resistance.

DR. BUTLER: Well, I assumed there were two years from --- and in fact there was some -- I can't remember which one it was but no, with the probability of tetracycline having a cross resistance to something else --- totally out of the blue --- had a cross resistance to something else.

CHAIRMAN MacMILLAN: I think the fluoroquinolone had a cross reaction with tetracycline where if you are resistant to the fluoroquinolone, you are also resistant to tet but not the reverse.

DR. BUTLER: Yeah. Well, and they were blown away by that one and it could happen the other way, so I think anything that's possible is possible.

CHAIRMAN MacMILLAN: Well, yeah, it's biology.

DR. BUTLER: Yeah.

(Participants away from microphones.)

DR. BUTLER: Well, you guys know better what bug is going to be --- what bug is going to be somewhere. The industry and the pharmaceutical company together would know what is the most likely bug and I wouldn't even call it a pathogen because a pathogen suggests it's causing the problem now independent of the antimicrobial resistance. So in other words, an indigenous bug, maybe that's what you could be using.

VOICE: I'm just reading the question. Which pathogen should ---

DR. BUTLER: Well, why don't we say it shouldn't necessarily be a pathogen as part of the question. How about using an indigenous bacterium instead of using a pathogen or it doesn't have to be a pathogen; it could be the other.

DR. REINSCHUESSA: Why don't we back up a little and just say what factors should be considered when modeling resistance. I mean, Randy, you mentioned a lot in your talk already. I don't know if we want to try to make a list of some of these for your report tomorrow or not. But just a quick list in my mind where temperature of the fish that are cultured. You know, the type of water and the water quality parameters in there.

DR. BUTLER: Including things like pH, saliency or

whatever.

DR. REINSCHUESSA: That's all water quality, yeah. Species of the fish, the type of aquaculture as in net pen or closed or ponds or the lined ponds versus earth and ponds. I'm giving the typist a second. Water quality, type of cultures and some target animal species.

Let's see, what else was I saying -- temperature. And then going along Randy's lines of -- that since human pathogens, food pathogens in fish are rare, not nonexistent but rare, then I'd say model and I don't if we call them innocent anymore but we call them a bystander and along with the pathogen that you're studying.

So now you're asking specifically which bystander to use, and that's where I'd say we've got to leave the until we get together with a lot of different micro people and start picking fish and organisms. I would consider taking something that's fairly easy to culture out, that is fairly ubiquitous in freshwater and fairly ubiquitous in saltwater as beginning organisms.

But I think we're going to need to do actual experiments before we even design a possible study plan for drug companies. I think we have to do some preliminary actual studies for this before we decide.

DR. BUTLER: So that would be a recommendation that the FDA group take a look at some sentinel organisms for

species.

DR. REINSCHUESSA: Or some extramural studies.

DR. BUTLER: Yeah.

DR. REINSCHUESSA: Because we're talking a lot of --

DR. BUTLER: --- which bug you might look at.

DR. REINSCHUESSA: But that's one for the future. I don't think that's one we're going to come up with by tomorrow. And then, with one other addendum, that if you come up with evidence that there is a human food safety pathogen that is found in the culture fish environment, then you also look at that, not necessarily something found on a filet that could have been put there in processing and all that.

DR. BUTLER: That's the salmonella from the catfish, for example.

DR. REINSCHUESSA: If you're finding them in the fish and the water, then it's worth going after that, but I wouldn't just start infecting fish with human pathogens as a possibility until you have real reason to do that.

DR. BUTLER: So the recommendation would be some sentinel indigenous species, maybe, plus --- is a pathogen that is typical or --

DR. REINSCHUESSA: Well, the one that they'd be using for the approval.

DR. BUTLER: Yes.

DR. REINSCHUESSA: I mean, you'd be doing anyway;

right?

DR. BUTLER: How do you do that, though? Oh, because it's the target organisms for the whatever, shrimp.

DR. KAZDA: --- where do they come from ---

DR. REINSCHUESSA: Darwin.

DR. KAZDA: --- indigenous by the type of water there ---

CHAIRMAN MacMILLAN: Well, and that's just it. If there is going to be some resident, homeothermic animal bacteria present, it's going to be because there are homothermic animals defecating into the water or into the water that eventually goes into the aquaculture pond.

So you can find E.coli in catfish ponds. You can find E.coli in the GI tract of catfish. They're just passing through, as best we can tell. It disappears as the temperature cools down. You can find salmonella.

George Flick from Virginia Tech -- I think that's where he is -- he's a food scientist. He's identified campylobacter in aquaculture ponds. He's identified salmonella, listeria monocytogenes. Probably all of the human food-borne pathogens that you could think of. I know there's klebcial in pneumonia in there.

Whether those bacteria are doing anything is another question and it would be interesting, from a scientific standpoint, to see if exposure of those bacteria, in very, very

low numbers -- they were so low in numbers, you couldn't even do an MPN and I don't know what that means, but his point was that there's very, very low numbers of those human pathogens in that warm water pond, aquaculture pond.

His view was, there's just no way that's going to be a human health hazard. But the point is that you can get those kinds of bacteria in that environment.

DR. KAZDA: I was just wondering --- you say that it's a species specific that, you know, certain type of fish would have certain type of bacteria, so I was just wondering how that happens, you know, why that one specie would be more prone to have one type of bacteria than others.

CHAIRMAN MacMILLAN: Well, you can make some broad differentiations that way. Marine fish are going to have vibrios. Freshwater fish are not going to have vibrios. Marine fish and freshwater fish could have salmonella but they would not necessarily have salmonella. We've checked our fish, for example for salmonella. It's not present.

But our water source is really unique in southern Idaho. Trout culture in Tennessee, it takes water from -- in fact, they may even get water from rivers. That's quite possible, or from drainage canals where cattle could poop. They could have salmonella.

DR. KAZDA: So it's the water quality.

CHAIRMAN MacMILLAN: It's the water quality. And so

--

DR. KAZDA: So that should be, actually, one way to monitor this whole thing. You know, the water that goes in, if you somehow culture the water or whatever, then you will probably be able to predict what the fish is going to be colonized.

DR. SIMMONS: The water quality is a major issue in the --- based on that. For example, in the --- part of the state, they ship --- every summer ---

DR. KAZDA: But it's also probably the temperature. I'm talking about wild fish now because I remember in Newfoundland, nobody goes to fish in August or whenever they say the fish is rotten and I was always questioning what they mean by rotten.

You know, I thought maybe because the fish --- or it's because the water temperature goes out, they become more of --- or whatever their fatty tissue so whatever --- the fish would taste rancid almost, but maybe -- they couldn't explain what they meant, rotten. But maybe it was that there was probably, by experience, some kind of outbreak of disease or whatever from that fish.

DR. REINSCHUESSA: --- of fish and then mammals. I mean, there are cow pathogens and there are people pathogens and there are pig pathogens, so they're all different species of mammals and we don't question why they would have different

bacterial flora.

VOICE: We're not going to give answers --

CHAIRMAN MacMILLAN: Well, we definitely not going to give answers, but I still struggle with the commensal because -- and I understand all of the reasons for trying to include it, but until you can put it into perspective, what do you do with them? And we're not going to be able to get at perspective --

DR. REINSCHUESSA: That would be a possible -- the role for the commensal would be the later surveillance.

CHAIRMAN MacMILLAN: Right. Well that's what I was going to say. The only way we can get, and it's not a perfect way to do it, but if we monitor the commensals. If we also have a program in place to monitor humans, which I guess we do -- is that right?

We monitor human pathogens that are -- so if we can some way or other, and maybe the modelers, that fellow today, for example, can put that into some sort of perspective so that we can use the information in a productive way. But you really have to include both of those entities, both of those studies, to try to ensure public health is protected.

DR. REINSCHUESSA: And so -- I mean, then, if you're saying to model --- if we're modeling a commensal, we want to look at it for post-market. I mean, we just have to come up with standards for even testing sensitivity in these organisms.

CHAIRMAN MacMILLAN: Well, and that's something

that's more easily done.

DR. REINSCHUESSA: I guess I'm being my own devil's advocate.

CHAIRMAN MacMILLAN: Well, relatively speaking.

DR. REINSCHUESSA: Well, real standards are not --- I mean, for real --

CHAIRMAN MacMILLAN: Right. But compared to trying to judge the impact on humans, that's far easier. So that's a little bit of information and maybe we just need to approach these pre-approval sorts of studies as it's an imperfect tool and it's an incomplete tool, but it's something that as long as we structure it right could be of value to the decision makers. Could be.

The problem I can see, if we don't put sufficient side boards on the information, then you're not going to know how to deal with it because you're always going to go back to that endpoint which is the human risk factor. We're probably not going to have a good measure of that for some period of time.

Well, it's quarter after five. We're supposed to go to 5:30. I don't know what everyone wants to do here, but what I would suggest is that we sleep on this. We're supposed to break out again tomorrow morning, and if you want to come up with some ideas yourselves, and I'll certainly try to do that just as a strawman to come out with tomorrow morning on how we

might craft some pre-approval studies.

And if that's agreeable to everyone, then we'll stand adjourned. If not, we can certainly continue talking. Any preferences? All right. We stand adjourned. Thank you, everyone.

(Whereupon, the meeting was adjourned, to reconvene Thursday, February 24, 2000 at 8:30 a.m. in the Randolph Room.)